Supplementary Materials

Genome-wide association and interaction studies of CSF T-tau/Aβ42 ratio in ADNI cohort

Jin Li[a], Qiushi Zhang[a,b], Feng Chen[a], Xianglian Meng[a], Wenjie Liu[a], Dandan Chen[a,b], Jingwen Yan[c,d,e], Sungeun Kim[c], Lei Wang[a], Weixing Feng[a], Andrew J. Saykin[c], Hong Liang[a,*], Li Shen[c,d,*], and for the ADNI

[a]College of Automation, Harbin Engineering University, 145 Nantong Street, Harbin, China, 150001
[b]College of Information Engineering, Northeast Dianli University, 169 Changchun Street, Jilin, China, 132012
[c]Center for Neuroimaging, Department of Radiology and Imaging Sciences, Indiana University School of Medicine, 355 West 16th Street, Suite 4100, Indianapolis, IN 46202
[d]Center for Computational Biology and Bioinformatics, Indiana University School of Medicine, 410 West 10th Street, Suite 5000, Indianapolis, IN 46202
[e]Department of BioHealth Informatics, Indiana University School of Informatics and Computing, Indianapolis, IN 46202

Comparative Study on Three CSF Phenotypes: T-tau, Aβ42, and the T-tau/Aβ42 ratio

In addition to the T-tau/Aβ42 ratio as the phenotype, we performed GWAS and GWIS on CSF T-tau alone and CSF Aβ42 alone. The results showed that the T-tau/Aβ42 ratio was a more sensitive marker than Aβ42 and T-tau in both GWAS and GWIS (see Table s1a and Table s1b).

In the single-maker analysis, while 24 SNPs exhibited genome-wide significance to the T-tau/Aβ42 ratio, only 6 and 3 SNPs showed genome-wide significance to Aβ42 and T-tau, respectively (Table s1a). Among the 24 significant SNPs related to T-tau/Aβ42 ratio, only 3 and 4 SNPs exhibited genome-wide significance to the T-tau and Aβ42 level, respectively (Table s2). According to Table s2, the loci from the *APOC1*, *APOE* and *TOMM40* region on Chromosome 19 are significantly associated with T-tau, Aβ42 and T-tau/Aβ42, and thus can potentially be driven by both the amyloid-β pathway and the tau pathway.

In the two-marker interaction effect analysis, while 307 pairs of SNPs showed statistically significant interaction effects on the T-tau/Aβ42 ratio (first threshold: Bonferroni-corrected p-value<0.05), 6 pairs of SNPs passed the first threshold on the T-tau level and none passed the first threshold on the Aβ42 level (Table s1b). Subsequently, only 7 pairs among 307 significant interaction pairs passed the second threshold (cell-size criterion: all the cell sizes in the 3-by-3 contingency table are required to be either more than 5 or equal to 0). Table s3 shows that none of the interactions identified for the T-tau/Aβ42 ratio are significantly associated with T-tau and Aβ42 alone.

In sum, all the GWAS and GWIS results indicated that, when CSF Aβ42 alone and T-tau alone show less power for detecting the risk variants, the T-tau/Aβ42 ratio has the potential to serve as a more powerful quantitative trait to identify significant variants (Tables s1-s3).

Table s1a. Numbers of GWAS results on different CSF phenotypes.

Phenotype / Test method	CSF $A\beta_{42}$		CSF T-tau		CSF T-tau/$A\beta_{42}$ ratio	
	Uncorrected p-value≤0.01	Corrected[a] p-value≤0.05	Uncorrected p-value≤0.01	Corrected[a] p-value≤0.05	Uncorrected p-value≤0.01	Corrected[a] p-value≤0.05
GWAS (Genotypic model)	5756	6	6166	3	6591	24

[a] Bonferroni corrected p-value≤0.05.

Table s1b. Numbers of GWIS results on different CSF phenotypes.

Phenotype / Test method	CSF $A\beta_{42}$		CSF T-tau		CSF T-tau/$A\beta_{42}$ ratio	
	Corrected[a] p-value≤0.05	Cell-size criterion[b]	Corrected[a] p-value≤0.05	Cell-size criterion[b]	Corrected[a] p-value≤0.05	Cell-size criterion[b]
GWIS (Linear regression)	0	0	6	0	**307**	**7**

[a] Bonferroni corrected p-value≤0.05.
[b] Cell-size criterion: all the cell size in 3-by-3 contingency table are required to be either more than 5 or equal to 0

Table s2. GWAS loci significantly associated with T-tau/Aß$_{42}$ and their associations with the T-tau and Aß$_{42}$ levels.

NO.	CHR	rs_No.	Gene	Single-marker p_value			Corrected p_value			R Square(T-tau/Aß$_{42}$)	
				T-tau/	T-tau	Aß$_{42}$	T-tau/ Aß$_{42}$	T-tau	Aß$_{42}$	Model$_a$	Model$_b$
1	19	rs4420638	APOC1	3.50E-2	1.96E-1	6.45E-42	**1.97E-21**	**1.10E-07**	**3.64E-36**	1.00E-01	1.00E-03
2	19	rs769449	APOE	6.41E-2	8.03E-1	2.26E-30	**3.62E-16**	**4.53E-05**	**1.27E-24**	9.10E-02	0
3	19	rs2075650	TOMM40	4.40E-1	2.92E-0	2.73E-22	**2.48E-11**	**1.63E-02**	**1.54E-16**	7.10E-02	0
4	19	rs157582	TOMM40	2.29E-1	3.56E-0	9.53E-24	**1.25E-10**	1.82E-01	**5.37E-18**	6.80E-02	1.00E-03
5	1	rs1337619	B3GALT2	3.04E-1	3.92E-0	1.47E-01	**1.70E-04**	1.98E-01	1	4.20E-02	3.10E-02
6	12	rs3020811	LRP6	1.24E-0	4.49E-0	3.30E-02	**6.90E-03**	1	1	3.00E-02	2.60E-02
7	9	rs2280302	FBP1	1.28E-0	4.17E-0	1.82E-01	**7.10E-03**	1	1	3.50E-02	2.60E-02
8	9	rs2280301	FBP1	1.37E-0	4.51E-0	1.86E-01	**7.60E-03**	1	1	3.50E-02	2.60E-02
9	10	rs1226579	ITGA8	1.85E-0	8.36E-0	1.98E-01	**1.03E-02**	1	1	3.40E-02	2.40E-02
10	10	rs7896076	ITGA8	1.87E-0	8.73E-0	1.94E-01	**1.04E-02**	1	1	3.40E-02	2.40E-02
11	10	rs1125363	ITGA8	1.91E-0	8.59E-0	1.99E-01	**1.07E-02**	1	1	3.40E-02	2.40E-02
12	1	rs1539581	ATP5F1	2.34E-0	1.37E-0	3.65E-01	**1.30E-02**	1	1	3.40E-02	2.40E-02
13	1	rs1012785	LPAR3	2.46E-0	1.03E-0	7.70E-02	**1.37E-02**	1	1	3.40E-02	2.30E-02
14	15	rs9806191	DAPK2	2.56E-0	9.98E-0	1.20E-02	**1.43E-02**	1	1	3.40E-02	2.30E-02
15	11	rs7129826	DBX1	2.99E-0	1.03E-0	1.61E-01	**1.67E-02**	1	1	3.30E-02	2.30E-02
16	21	rs1191098	S100B	3.17E-0	1.06E-0	2.07E-01	**1.77E-02**	1	1	3.30E-02	2.30E-02
17	21	rs1981331	S100B	3.19E-0	9.94E-0	1.75E-01	**1.78E-02**	1	1	3.30E-02	2.30E-02
18	3	rs9872004	AADACL1	3.26E-0	1.01E-0	1.81E-01	**1.81E-02**	1	1	3.30E-02	2.30E-02
19	1	rs1702763	ATP5F1	3.26E-0	1.02E-0	2.07E-01	**1.82E-02**	1	1	3.30E-02	2.30E-02
20	1	rs6662771	SGIP1	3.44E-0	1.04E-0	1.76E-01	**1.92E-02**	1	1	3.30E-02	2.30E-02
21	11	rs1279720	DLG2	3.71E-0	2.70E-0	1.38E-01	**2.06E-02**	1	1	3.30E-02	2.50E-02
22	18	rs6506440	ARHGAP2	7.51E-0	6.42E-0	1.19E-01	**4.14E-02**	1	1	3.20E-02	2.60E-02
23	2	rs6541929	CNTNAP5	7.64E-0	2.45E-0	2.50E-02	**4.21E-02**	1.29E-01	1	3.20E-02	2.70E-02
24	2	rs1726732	CNTNAP5	8.23E-0	2.15E-0	2.90E-02	**4.53E-02**	1.14E-01	1	3.10E-02	2.80E-02

The bonferroni corrected p-values (< 0.05) are shown in bold.

[a] Model: Percent of additional variance in T-tau/Aß$_{42}$ level explained by the main effect of SNPs after accounting for age, gender, and diagnosis.

[b] Model: Percent of additional variance in T-tau/Aß$_{42}$ level explained by the main effect of SNPs after accounting for age, gender, diagnosis, and the *APOE* genotype.

Table s3. GWIS locus pairs significantly associated with T-tau/Aß$_{42}$ and their associations with the T-tau and Aß$_{42}$ levels.

SNP 1					SNP 2					SNP 1 by SNP 2 Interaction					
Chr	SNP	Uncorrected p-value			Chr	SNP	Uncorrected p-value			Uncorrected p-value			Bonferroni corrected p-value		
		T-tau/Aß$_{42}$	Aß$_{42}$	T-tau			T-tau/Aß$_{42}$	Aß$_{42}$	T-tau	T-tau/Aß$_{42}$	Aß$_{42}$	T-tau	T-tau/Aß$_{42}$	Aß$_{42}$	T-tau
7	rs6467419	3.18E-03	9.00e-02	1.00e-02	7	rs1514061	6.24E-02	8.00e-02	5.10E-01	**8.35E-10**	5.50E-02	3.51E-05	**1.81E-02**	1	1
16	rs4453471	5.19E-03	8.60E-01	1.00E-02	7	rs1514061	6.24E-02	8.00E-02	5.10E-01	**1.97e-10**	3.16E-02	5.17E-05	**4.30E-03**	1	1
12	rs7303599	1.21E-03	9.50E-01	1.00E-02	14	rs7146454	1.94E-03	7.00E-02	1.00E-02	**5.76E-11**	5.70E-03	1.94E-08	**1.30E-03**	1	1
12	rs7303599	1.21E-03	9.50E-01	1.00E-02	9	rs167396	1.20E-01	3.00E-02	4.80E-01	**6.91E-10**	2.86E-02	4.09E-07	**1.50E-02**	1	1
14	rs12894119	6.83E-03	2.00E-02	1.10E-01	7	rs1482548	8.11E-01	1.80E-01	7.50E-01	**2.95E-10**	1.26E-05	2.57E-07	**6.40E-03**	1	1
13	rs9550406	1.30E-03	2.00E-02	2.00E-02	8	rs6471951	1.78E-03	9.00E-02	4.00E-02	**1.49E-09**	2.91E-03	9.79E-06	**3.24E-02**	1	1
10	rs4881147	6.65E-04	2.00E-01	1.80E-03	21	rs211953	1.60E-02	9.60E-01	4.00E-02	**3.03E-10**	4.85E-04	2.93E-08	**6.60E-03**	1	1

Literature review of significant loci identified in this work

Table s4a and Table s4b summarize the prior results on genes related to the significant loci reported in this work. While Table s4a focuses on our GWAS findings, Table s4b focuses on our GWIS findings

Table s4a. Literature survey results: Previously known associations regarding our GWAS findings.

NO.	Gene	Study	Example Paper	Phenotype	Finding
1	*APOC1*	GWAS	(Souza, Araujo, Costa, Oliveira, & Alzheimer's Disease Neuroimaging, 2016)	CSF Amyloid-$ß_{42}$	rs439401 in the intergenic region of *LOC100129500* and *APOC1*
2	*APOE*	CSF biomarker study	(Smach et al., 2008) (Tosun et al., 2010)	CSF Amyloid-$ß_{42}$ CSF T-tau	$Aß_{42}$ was decreased and t-tau increased in AD patients. *APOE* e4+ AD patients had lower $Aß_{42}$ than e4- patients.
3	*TOMM40*	GWAS	(Souza et al., 2016)	CSF Amyloid-$ß_{42}$	rs2075650 in *TOMM40* (replicated in our GWAS)
4	*LRP6*	Cell culture and mouse model studies	(Zhang, Bahety, & Ee, 2015)	Tau phosphorylation	LRP5/6-mediated Wnt signaling to reduce tau phosphorylation
			(Liu et al., 2014)	Amyloid-$ß_{42}$ Amyloid-$ß_{40}$	LRP6-mediated Wnt signaling to down-regulated amyloid-β
5	*S100B*		(Esposito et al., 2008)	Tau	S100B induces tau protein hyperphosphorylation
			(Mori et al., 2010)	Amyloid-ß (Aß)	Overexpression of S100B accelerates AD-like
6	*DLG2*	Quantitative proteomics	(Hondius et al., 2016)	Hippocampus tissue	DLG2 exhibits an early-up, late-down expression pattern in protein levels in the hippocampus during AD pathology
7	*CNTNAP5*	GWAS	(Schott et al., 2016)	Posterior cortical atrophy (PCA)	rs76854344 near *CNTNAP5*
8-17	Our literature review did not identify studies showing the associations to the AD relevant phenotypes for the following genes: *B3GALT2, FBP1, ITGA8, ATP5F1, LPAR3, DAPK2, DBX1, AADACL1, SGIP1,* and *ARHGAP28*.				

Table s4b. Literature survey results: Previously known associations regarding our GWIS findings.

NO.	Gene	Study	Example Paper	Phenotype	Finding
1	*PLXNA4*	GWAS	(Jun et al., 2014)	Diagnosis, phospho-tau，total-tau	*PLXNA4* SNP rs277470 increased tau phosphorylation
2	*CDH13*	Set-based GWAS	(Kohannim et al., 2012)	Temporal lobe volume	Discovered 22 genes including *CDH13* significantly associated with temporal lobe volume
3	*ADIPOR2*	Cell culture study	(Chan et al., 2012)	Amyloid-ß (Aß)	Adiponectin was protective against Aß induced neuronal cytotoxicity under oxidative stress
4	*ADSSL1*	Candidate gene	(Rosenthal et al., 2012)	LOAD diagnosis, Amyloid-ß (Aß)	Haplotype analysis reported significant association in *ADSSL1* (an Aß toxicity modifier genes)
5	*GSN*	Plasma biomarkers	(Peng, Jia, & Qin, 2015)	Relative GSN = GSN/ (Aß42 + Aß40)	Relative GSN for AD diagnosis: AUC = 0.66, sensitivity = 54.9%, specificity = 75.2%.
		Mouse model	(Yang et al., 2014)	GSN, Aß42, Aß40	Gelsonlin (GSN) inhibits Aß fibrillation, solubilizes preformed Aβ fibrils, and helps in its clearance from the brain
6	*PITRM1*	Yeast & mouse studies	(Brunetti et al., 2016)	Amyloid-ß (Aß)	PITRM1 is associated with Aß degradation
7-11	Our literature review did not identify studies showing the associations to the AD relevant phenotypes for the following genes: *INHBA, NIN, MTUS2, RLBP1L1,* and *CXADR*.				

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